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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/523,886	03/13/00	GRDINA D	P-01904US1

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EXAMINER	
CHEN, S	
ART UNIT	**PAPER NUMBER**
1633	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

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PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary	Application No. 09/523,886	Applicant(s) GRDINA ET AL.	
	Examiner Shin-Lin Chen	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-31 is/are pending in the application.

4a) Of the above claim(s) 14-22 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-13 and 23-31 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5,7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

1. If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph.

Election/Restriction

2. Applicant's election without traverse of group V, claims 1-13 and 23-31, in Paper No. 9 is acknowledged.

3. Claims 14-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

Claims 1-31 are pending. Claims 1-13 and 23-31 are under consideration.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 8 recites the limitation "said compound" in line 1. There is insufficient antecedent basis for this limitation in the claim. Similarly, claims 11-13 recite the limitation "said compound" and thus lack sufficient antecedent basis for this limitation in the claims.

6. Claim 9 recites the limitation "said derivative" in line 1. There is insufficient antecedent basis for this limitation in the claim.

7. Claim 10 recites the limitation "said derivative" in line 1. There is insufficient antecedent basis for this limitation in the claim.

8. Claims 1-13 and 23-31 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See M.E.P.. § 2172.01. The omitted steps are: whether the phosphorothioate or active metabolite thereof reduces the number of metastases after administering into the animal (claims 1-13 and 23-29), whether the phosphorothioate or active metabolite thereof inhibits metastases in an animal after administering into said animal (claim 30), and whether the phosphorothioate or active metabolite thereof prevents metastases in an animal after administering into said animal (claim 31).

9. Claims 1-13 and 23-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "active metabolite thereof" in claims 1, 23, 30 and 31 is vague and renders the claims indefinite. The specification defines the phrase "active metabolite" as "according to its

ordinary meaning among those of skill in the art, i.e., to refer to a product of intermediary metabolism that possesses an activity. It is unclear what "activity" is intended by the applicants in the present application. Claims 2-13 and 24-29 depend on either claim 1 or claim 23 but fails to clarify the indefiniteness.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 7-9 and 11-13 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Milas et al., 1984 (IDS-C51).

Claims 1, 7-9 and 11-13 are directed to a method for reducing the number of metastases in an animal having a primary tumor, such as a sarcoma or a carcinoma, by administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof, such as WR-2721. Claims 12 and 13 specify the route of administration is intravenous, intraperitoneal etc., and the phosphorothioate or active metabolite thereof is formulated into solutions, suspensions, tablets etc, respectively.

Milas teaches WR-2721 greatly reduces the spontaneous metastases induced by cyclophosphamide (CY) and whole body irradiation (WBI) in mice with fibrosarcoma injected i.v. into said mice. WR-2721 was given intraperitoneal (i.p.) at a dose of 400mg/kg before WBI or CY injection and WR-2721 was capable of significant protection against metastases enhancement induced by CY and WBI by preventing radiation- or CY-caused immuno-suppression. Thus, claims 1, 7-9 and 11-13 are clearly anticipated by Milas.

12. Claims 1, 8, 9, 12, 13, 30 and 31 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Flora et al., 1996 (IDS-C9).

Claims 1, 8, 9, 12 and 13 are directed to a method for reducing the number of metastases in an animal having a primary tumor by administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof. Claims 12 and 13 specify the route of administration is intravenous, intraperitoneal etc., and the phosphorothioate or active metabolite thereof is formulated into solutions, suspensions, tablets etc, respectively. Claims 30 and 31 are directed to a method for inhibiting or preventing metastases in an animal having a primary tumor by administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof.

Flora teaches the thiol N-acetylcysteine (NAC) is a promising cancer chemopreventive agent which acts through a variety of mechanism, including its nucleophilic and antioxidant properties. NAC inhibited lung metastases when added to the medium of cancer cells before

their i.v. injection into nude mice, and NAC showed significant protective effects and considerably prolonged survival of mice (e.g. abstract). NAC is an amino alkylphosphorothioate compound. Thus, claims 1, 8, 9, 12, 13, 30 and 31 are clearly anticipated by Flora.

13. Claims 1, 7-9, 12, 13, 30 and 31 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Hasegawa et al., 1998 (International Journal of Cancer, Vol. 76, No. 6, p. 812-816).

Claims 1, 7-9, 12 and 13 are directed to a method for reducing the number of metastases in an animal having a primary tumor, such as a sarcoma or a carcinoma, by administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof. Claims 12 and 13 specify the route of administration is intravenous, intraperitoneal etc., and the phosphorothioate or active metabolite thereof is formulated into solutions, suspensions, tablets etc, respectively. Claims 30 and 31 are directed to a method for inhibiting or preventing metastases in an animal having a primary tumor by administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof.

Hasegawa teaches injecting intraperitoneally the matrilysin -specific antisense phosphorothioate oligonucleotide into nude mice every day from 1 day before to 10 day after the intrasplenic injection of WiDr cells (human colon carcinoma cells), and the formation of the metastatic tumor nodules was strongly inhibited in a dose-dependent manner. The administration of the antisense oligonucleotide significantly reduced the number of metastatic tumor nodules in

the liver, and the antisense oligonucleotide did not inhibit tumor growth (e.g. abstract, p. 813). The antisense phosphorothioate oligonucleotide is considered an active metabolite of phosphorothioate. Thus, claims 1, 7-9, 12, 13, 30 and 31 are clearly anticipated by Hasegawa.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 2-7, 10, 23 and 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albini et al., 1995 (IDS-C1), in view of Golub, 1998 (US Patent No. 5,837,696), Grdina et al., 1995 (IDS-C15) and Antras-Ferry et al., 1997 (IDS-C2).

Claims 2-7, 10, 23 and 25-29 are directed to a method for reducing the number of metastases in an animal having a primary tumor, such as a sarcoma or a carcinoma, by administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof, and further comprising monitoring the ability of the subcytoprotective dose of the phosphorothioate or active metabolite to reduce metastases via measuring the activity of matrix metalloproteinase (MMP), such as MMP-2 or MMP-9, or the stimulation of MnSOD gene expression. Claims 2-5 specify the dose as recited in the claims, such as about 10 mg/kg to about 150 mg/kg. Claim 6 specifies the animal is a human. Claim 10 specifies the active derivative is the disulfide form.

Albini teaches that "thiol N-acetylcysteine (NAC) is currently considered one of the most promising cancer chemopreventive agents by virtue of its multiple and coordinated mechanisms affecting the process of chemical carcinogenesis", and "NAC was efficient in inhibiting the chemotactic and invasive activities of tumor cells of human (A2058 melanoma) and murine origin (K1735 and B16-F10 melanoma cells as well as C87 Lewis lung carcinoma cells). NAC probably affects the process of tumor-cell invasion and metastasis via inhibition of gelatinases, such as MMP-2 and MMP-9, by its sulfhydryl group (e.g. abstract). The growth of the local tumor was not affected by NAC administration in the experiment using LLC Lewis lung carcinoma cells, and NAC (0.5 g to 2g/kg) reduces the number of lung metastases in C57BL/6 mice 4 weeks after injection of B16-BL6 murine melanoma cells (e.g. p. 125, figure 5).

Albini does not specifically teach using the dose as cited in the claims 2-5, such as 10mg/kg to 150mg/kg, using a human for the claimed method, using disulfide form of the phosphorothioate, and measuring the activity of MMP-2, MMP-9, or MnSOD to monitor the ability of the phosphorothioate or active metabolite thereof.

Golub teaches a method of inhibiting cancer growth, including cellular proliferation, invasiveness, or metastasis, in a mammal by administering to said mammal a cancer-inhibitory amount of a tetracycline compound (e.g. 0.1mg/kg/day to 30mg/kg/day), such as CMT-3, and said tetracycline compound specifically inhibit expression of gelatinase A or gelatinase B (MMP-2 or MMP-9) (column 7, 14). Golub also teaches that MMP expression, especially gelatinase expression, is associated with cancer invasiveness or metastasis, and CMT-3 inhibits the expression of MMP-2 and MMP-9 in cancer cells *in vitro*. Golub suggests the method set forth above can be used as a prophylactic treatment by administering the tetracycline compound to a mammal after detection of a gene product or metabolite associated with predisposition to a cancer (e.g. column 6).

Antras-Ferry teaches that Oltipraz (4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione) (OPZ) is a potent chemoprotective agent against chemical induced carcinogenesis in several animal model and OPZ induces the transcription of the manganese superoxide dismutase (MnSOD) in a dose-dependent manner (e.g. abstract).

Grdina teaches thiol and disulfide metabolites of phosphorothioate WR-2721 are linked to both its anti-cytotoxic and anti-mutagenic mechanisms of action (e.g. title). WR-2721 and

associated aminothiol compounds are radioprotectvie agents that provide protection against radiation induced mutagenesis (e.g. p. 767).

It would have been obvious for one of ordinary skill at the time of the invention to use the dose range cited in claims 2-5 for the claimed method because Golub teaches using a cancer-inhibitory amount of a tetracycline compound (e.g. 0.1mg/kg/day to 30mg/kg/day) to inhibit metastasis of cancer cells, and the range 0.1mg/kg to 30mg/kg overlap with the range 10mg/kg to 150mg/kg and further determining effective dose is routine optimization of a result-effective variable and is obvious to a person of ordinary skill. It would have been obvious for one of ordinary skill at the time of the invention to monitor the ability of the phosphorothioate to reduce metastasis by measuring the activity of MMP-2 or MMP-9 because NAC probably affects the process of tumor-cell invasion and metastasis via inhibition of gelatinases, such as MMP-2 and MMP-9, by its sulfhydryl group as taught by Albini, and Golub teaches that MMP expression, especially gelatinase expression, is associated with cancer invasiveness or metastasis, and suggests detection of MMP gene products for a prophylactic treatment using tetracycline compound. It also would have been obvious for one of ordinary skill at the time of the invention to monitor the ability of the phosphorothioate to reduce metastasis by measuring the stimulation of MnSOD gene expression because both NAC and OPZ are chemoprotective agents and OPZ can induce MnSOD gene expression. It was known in the art WR-2721 can decrease the metastatic spread in tumor bearing mice after irradiation (Ullrich et al., 1976, IDS-C52) and Albini teaches NAC is efficient in inhibiting the chemotactic and invasive activities of tumor

cells of human (A2058 melanoma) and murine origin. Since both NAC and WR-2721 are phosphorothioate having effect in inhibiting metastasis and both thio and disulfide forms of WR-2721 are linked to its anti-cytotoxic and anti-mutagenic mechanisms of action, it would have been obvious for one of ordinary skill that the disulfide form of WR-2721 could also have inhibiting effect on metastasis.

One having ordinary skill at the time of the invention would have been motivated to do so in order to obtain an efficient amount of the phosphorothioate or active metabolite thereof, including disulfide form, to reduce the number of metastasis in a tumor bearing animal as taught by Albini, Golub and Grdina, and to monitor the effectiveness of the phosphorothioate and active metabolite thereof in reducing the number of metastasis in tumor bearing animals by measuring the activity of MMP-2 and MMP-9, and gene expression of MnSOD as taught by Albini, Golub and Antras-Ferry with reasonable expectation of success.

16. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Albini et al., 1995 (IDS-C1), in view of Gately et al., 1997 (IDS-C13).

Claim 24 is directed to a method for reducing the number of metastases in an animal having a primary tumor by administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof, and further comprising monitoring the ability of the subcytoprotective dose of the phosphorothioate or active metabolite to reduce metastases via measuring the level of angiostatin stimulation.

Albini teaches that "thiol N-acetylcysteine (NAC) is currently considered one of the most promising cancer chemopreventive agents by virtue of its multiple and coordinated mechanisms affecting the process of chemical carcinogenesis", and "NAC was efficient in inhibiting the chemotactic and invasive activities of tumor cells of human (A2058 melanoma) and murine origin (K1735 and B16-F10 melanoma cells as well as C87 Lewis lung carcinoma cells). NAC probably affects the process of tumor-cell invasion and metastasis via inhibition of gelatinases, such as MMP-2 and MMP-9, by its sulfhydryl group (e.g. abstract). The growth of the local tumor was not affected by NAC administration in the experiment using LLC Lewis lung carcinoma cells, and NAC (0.5 g to 2g/kg) reduces the number of lung metastases in C57BL/6 mice 4 weeks after injection of B16-BL6 murine melanoma cells (e.g. p. 125, figure 5).

Albini does not specifically teach measuring the stimulation of angiostatin to monitor the ability of the phosphorothioate or active metabolite thereof.

Gately teaches angiostatin inhibits angiogenesis *in vitro* and *in vivo* and suppresses the growth of Lewis lung carcinoma metastases.

It would have been obvious for one of ordinary skill at the time of the invention to measure the stimulation of angiostatin for monitoring the ability of the phosphorothioate or active metabolite thereof because angiostatin was known to suppress lung carcinoma metastasis and the stimulation of angiostatin would indicate the reduction of metastases.

One having ordinary skill at the time of the invention would have been motivated to do so in order to monitor the effectiveness of the phosphorothioate and active metabolite thereof in

reducing the number of metastasis in tumor bearing animals by measuring stimulation of angiostatin with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, whose telephone number is (703) 305-3015.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

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